UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,105	10/12/2005	Toon Laeremans	A0848.70011US00	9110

23628 7590 01/10/2008
WOLF GREENFIELD & SACKS, P.C.
600 ATLANTIC AVENUE
BOSTON, MA 02210-2206

EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
01/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,105	LAEREMANS ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,16-34 and 36-45* is/are pending in the application.

4a) Of the above claim(s) *10-12,16-18,20,22,24,26,28,30,32,34 and 37-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,13,19,21,23,25,27,29,31,33,36 and 42-45* is/are rejected.

7)☒ Claim(s) *2* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 October 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-13, 16-34 and 36-45 are pending.

2. Applicant's election with traverse of Group 6, Claims 1-9, 13, 19, 21, 23, 25, 27, 29, 31, 33, 36, and 42-45, drawn to an anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one single domain antibody directed against EGFR, an anti-EGFR polypeptide of SEQ ID NO: 6, a kit comprising said anti-EGFR polypeptide, a method for preparing a medicament comprising combining said anti-EGFR and a carrier, and a therapeutic composition comprising said polypeptide, filed 11/9/07, is acknowledged.

The traversal is on the grounds that Applicant has identified EGFR-binding polypeptides that have unique properties, which polypeptides have a special technical feature. It is noted that neither the International Searching Authority nor the International Preliminary Examining Authority made any unity of invention objection in the international phase of this application. According to MPEP § 1850, "From the preceding paragraphs it is clear that the decision with respect to unity of invention rests with the International Searching Authority or the International Preliminary Examining Authority." MPEP § 1850, II. DETERMINATION OF "UNITY OF INVENTION". Therefore it is respectfully submitted that there is decision to be made as to any lack of unity.

Even if the lack of unity of invention is maintained, Applicant requests reconsideration of the grouping of the claims on the basis that product claims should be examined together with claims to processes of making the product and claims to processes of using the product. Specifically, MPEP 1850 states in section IIIA, "Combinations of Different Categories of Claims" that "The method for determining unity of invention under PCT Rule 13 shall be construed as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application: (A) In addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of the said product, and an independent claim for a use of the said product ...." Thus, Applicant asserts that claims to use of the products of Group 6 should be included in the elected invention. It further is noted that SEQ ID NO:6, also known as Nanobody Ial (see Table 5, page 53 of the specification), is a Nanobody that blocks EGF binding to EGFR, and thus is representative of a class of Nanobodies. Applicant respectfully submits that it would not represent

an undue burden of searching and examination to examine as a group Nanobodies that block EGF binding to EGFR, of which SEQ ID NO: 6 is representative.

This is not found persuasive because of the reasons set forth in the restriction mailed May 7, 2007. The inventions listed as Groups 1-30 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Consistent with the International Search Report, the invention of Group I was to have no special technical feature that defined the contribution over the prior art 20020058033 publication (PTO1449), WO 96/34096 publication and Muyldermans et al.

The 20020058033 publication (PTO1449) teaches human single chain antibody that binds specifically to anti-epidermal growth factor receptor (EGFR), see paragraph 0045, in particular). The 20020058033 publication teaches a composition comprising the human single chain antibody against EGFR and the composition is useful for therapeutic and/or diagnostic of cancer (see paragraph 0016-0017, in particular).

The invention differs from the teachings of the reference only an anti-EGFR polypeptide comprising least one single domain antibody directed against EGFR.

WO 96/34096 publication (published October 1996; PTO 892) teaches an anti-epidermal growth factor receptor (EGFR) polypeptide such as human antibody to EGFR comprising at least one domain direct against EGFR (see entire document, page 14, line 25, claim 24 of the publication, in particular). The antibody is non-immunogenic and useful for treating cancer (see claim 47, in particular).

Muyldermans et al (J Molecular Recognition 12: 131-140, 1999; PTO 892) teach a method of making various single domain antibody direct against various antigens such as lysozyme, tetanus toxoid (see entire document, page 136, in particular). Muyldermans et al teach a minimal size of antigen-binding fragment would have several biotechnological and medical advantages: for example in cases where a lower immunogenicity, a more rapid clearance from blood and less non-specific binding or an improved penetration in dense tissues is required (see paragraph bridging page 135 and 136, in particular). Natural occurring antibody binding portion such as VHH (single domain) heavy chain antibody isolated from camels, or llamas is the smallest antigen binding fragment (see page 132, col. 2, Figure 1B-C, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make any single domain antibody from camelidate VHH as taught by

Muyldermans et al that binds specifically to epidermal growth factor receptor (EGFR) as taught by the WO 96/34096 publication or the 20020058033 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Muyldermans et al teach a minimal size of antigen-binding fragment would have several biotechnological and medical advantages: for example in cases where a lower immunogenicity, a more rapid clearance from blood and less non-specific binding or an improved penetration in dense tissues is required (see paragraph bridging page 135 and 136, in particular). WO 96/34096 publication teaches human antibody is non-immunogenic and useful for treating cancer (see claim 47, in particular). The 20020058033 publication teaches composition comprising the human single chain antibody against EGFR is useful for therapeutic and/or diagnostic of cancer (see paragraph 0016-0017, in particular).

Since Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have single general inventive concept and lack unity of invention.

Therefore, the requirement of Group 6 (now claims 1-10, 17-18, 21-23, 25-27, 46, 53-60, 69-70, 72-74, and 78) and Groups 1-5 and 7-30 is still deemed proper and is therefore made FINAL.

With respect to the argument that the product claims should be examined together with claims to processes of making the product and claims to processes of using the product under unity of invention practice, it is noted that applicants' inventions *do not* contribute a special technical feature when viewed over the prior art; they do not have single general inventive concept and therefore *lack unity of invention.*

However, when applicant's inventions contribute a special a special technical feature when viewed over the prior art and therefore *has unity of invention*, then under unity of invention practice as it applies to cases filed under 35 U.S.C. 371, unity of invention between different categories of inventions will only be found to exist if specific combinations of inventions are present. Those combinations include:

A) A product and a special process of manufacture of said product.

B) A product and a process of use of said product.

C) A product, a special process of manufacture of said product, and a process of use of said product.

D) A process and an apparatus specially designed to carry out said process.

E) A product, a special process of manufacture of said product, and an apparatus specially designed to carry out said process.

The allowed combinations under unity of invention practice do not include multiple products and multiple methods of using said products see MPEP § 1850. In this case, unity of invention does not apply because of the lack of unity of invention over prior art discussed above.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

3. Claims 10-12, 16-18, 20, 22, 24, 26, 28, 30, 32, 34, and 37-41 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 1-9, 13, 19, 21, 23, 25, 27, 29, 31, 33, 36, and 42-45, drawn to an anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one single domain antibody directed against EGFR, an anti-EGFR polypeptide of SEQ ID NO: 6, a kit comprising said anti-EGFR

polypeptide, a method for preparing a medicament comprising combining said anti-EGFR and a carrier, and a therapeutic composition comprising said polypeptide, are being acted upon in this Office Action.

5. Claim 2 is objected to as the claims encompass non-elected embodiments.

6. Claims 2-9, 44 and 45 are objected to because "A" should have been "The" for said dependent claims.

7. The drawings are objected to because Figures 1-4 are missing. The submitted Figures are labeled as Figure 5-1 and Figure 5-2. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 3-9, 13, 19, 21, 23, 25, 27, 29, 31, 33, 36, and 42-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for an isolated anti-Epidermal Growth Factor Receptor (EGFR) single domain antibody comprising the amino acid sequence of SEQ ID NO: 6, a humanized Epidermal Growth Factor Receptor (EGFR) single domain antibody comprising the amino acid sequence of SEQ ID NO: 13, a composition comprising the isolated anti-Epidermal Growth Factor Receptor (EGFR) single domain antibody comprising the amino acid sequence of SEQ ID NO: 6 and a carrier for targeting EGFR, a kit comprising the isolated anti-Epidermal Growth Factor Receptor (EGFR) single domain antibody comprising the amino acid sequence of SEQ ID NO: 6 for detecting EGFR polypeptide and bispecific single domain antibody that binds specifically to EGFR and serum albumin comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 27-40, **does not** reasonably provide enablement for (1) any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR as set forth in claims 1, and 5-7 for treating and/or *preventing* and/or alleviating any disorders, any disorders such as any cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung, (2) any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR further comprising any single domain antibody directed against any serum protein, (3) anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR further comprising any single domain antibody as set forth in claim 4, (4) any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR wherein said at least one single domain antibody is any homologous sequence, any functional portion, or any functional portion of any homologous sequence of any full length single domain antibody, (5) any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR wherein said at least one single domain antibody is any homologous sequence, any functional portion, or any functional portion of any homologous sequence of any full length anti-EGFR polypeptide, (6) any kit comprising any anti-Epidermal Growth Factor Receptor EGFR)

polypeptide comprising at least any one single domain antibody directed against any EGFR and Epidermal Growth factor or any fragment thereof, (7) a method for the preparation of a medicament comprising any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR and a carrier, (8) any composition comprising any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR and a suitable pharmaceutical vehicle, (9) any kit comprising any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR as set forth in claims 36, 42, and (10) any therapeutic composition comprising any VHH which inhibits the growth of human tumor cells by said VHH binding to Epidermal Growth factor receptor of said human tumor cells and (b) any anti-neoplastic agent as set forth in claims 42-45. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claim 1 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR.

Claim 3 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least any one single domain antibody directed against EGFR further comprising at least one of any single domain antibody directed against any serum protein.

Claim 4 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least any one single domain antibody directed against EGFR further comprising at least one of any single domain antibody directed against IFN-gamma, TNF-alpha, TNF-alpha receptor, or IFN-gamma receptor.

Claim 5 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least two single domain antibody directed against EGFR.

Claim 6 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least any one single domain antibody directed against EGFR from *Camelidae* VHH.

Claim 7 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least any one humanized *Camelidae* VHH single domain antibody directed against EGFR.

Claim 8 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR wherein said at least one single domain antibody is any homologous sequence, any functional portion, any functional portion of any homologous sequence of the full length single chain antibody.

Claim 9 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR wherein the anti-EGFR polypeptide is any homologous sequence, any functional portion, any functional portion of any homologous sequence of the full length single chain antibody.

Claim 13 encompasses a kit comprising any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR and EGFR, or any fragment thereof.

Claims 19, 21, 23, 25, 27, 29 and 31 encompass a method for preparing a medicament comprising combining any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR and a carrier.

Claim 33 encompasses a composition comprising any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR and a suitable pharmaceutical vehicle.

Claims 36 and 42 encompass a kit comprising any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR.

Claims 43-45 encompass a therapeutic composition comprising any VHH which inhibits the growth of human tumor cells by said VHH binding to EGFR and any anti-neoplastic agent.

Enablement is not commensurate in scope with how to make and use any anti-EGFR polypeptide mentioned above.

The specification discloses only isolated single domain antibody VHH from *Camelidae* that binds specifically to Epidermal Growth Factor Receptor (EGFR) such as the ones shown in Table 4 wherein the antibody comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 1-22. The specification discloses these single domain antibodies selected for binding to EGFR and for the ability to internalize through cell surface EGFR, see page 50. The specification discloses humanized VHH represented by SEQ ID NO: 13, see page 15, lines 9-21. The specification further discloses the isolated single domain antibody VHH from *Camelidae* that binds to EGFR further comprising a single domain antibody VHH that binds to serum albumin corresponds to a sequence selected from the group consisting of SEQ ID NO: 27-40 as shown in Table 5. There is no disclosure whether any such anti-EGFR can treat, much less *prevent* any disorders relating to any cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung.

The specification does not teach how to make and use any anti-EGFR polypeptide mentioned above without the amino acid sequence. An anti-EGFR polypeptide without the amino acid sequence has no structure, much less function. Even if the single domain antibody corresponds to SEQ ID NO: 6, the term "at least one" encompasses one or more single domain antibody directed against EGFR. There is insufficient guidance as to which other single domain antibody is part of the anti-EGFR polypeptide. Further, the term "comprising" is open-ended. It expands the undisclosed sequence of the single domain antibody directed agonist EGFR to include additional amino acids at either or both ends. Based on the definition of "single domain antibody", the specification defines single domain antibodies include, but not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies and single domain scaffolds other than those derived from antibodies. Single domain antibodies may be any of the art, or any future single domain antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, goat, rabbit, bovine, see page 13, lines 13-19. As such, the structure of the anti-EGFR polypeptide without the amino acid sequence is not enabled. Further, there is a lack of *in vivo* working examples demonstrating any such anti-EGFR polypeptide can treat, much less preventing any disorder relating to cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung.

Rudikoff et al (Proc Natl Acad Sci U S A 79(6): 1979-83, March 1982; PTO 892) teach a single amino acid substitution from glutamic acid to alanine at position 35 in the first

hypervariable or complementarity-determining region of an antibody resulted altered binding specificity of the antibody (See abstract, in particular).

Schlaeppi et al (J Cancer Res Clin Oncol 125: 336-342, 1999; PTO 892) teach substitutions of three residues (Q87R, G88K, Q89K) located on the major surface loop β5 to β6 of VEGF, resulted in complete loss of binding (see abstract, in particular). Schlaeppi et al further teach that antibody that binds to the dimeric form of VEGF is conformational dependent (see abstract, in particular).

Winkler et al (J Immunology 165: 4505-4514, 2000; PTO 892) teach a single amino acid changes in the variable region of any antibody may substantially change the binding specificity of antibody (see abstract, in particular).

Zhu et al (Investigational New Drugs 17: 195-212, 1999; PTO 892) teach despite high sequence homology (i.e. 85%) between mouse FLK-1 and its human homolog, KDR, none of the blocking anti-KDR antibodies produced cross-reacts with Flk-1. Consequently, tumors grown in mice, which recruit the mouse vasculature, are not appropriate models to evaluate the anti-angiogenesis therapy *in vivo* (see page 201, col. 2, last paragraph, in particular). Given the lack of guidance as to structure associated with binding specificity of such anti-EGFR polypeptide, the lack of direction or working examples, the breadth of the claims, which encompass innumerable possible proteins, and the amount of experimentation required to determine each possible species individually, it would require undue experimentation to use the invention in a manner commensurate in scope with the claims.

With respect to claim 3, the specification discloses only single domain heavy chain antibody VHH that binds to serum albumin alone or fused to single domain heavy chain antibody VHH that binds to EGFR. As such, the binding specificity of any anti-EGFR polypeptide comprising at least one single domain antibody directed against any serum protein and at least one single domain antibody is not enabled.

With respect to claim 6, the specification discloses single domain antibodies were raised in llamas. The specification defines VHH molecule can be derived from antibodies raised in *Camelidae* species, for example in camel, dromedary, llama, vicuña, alpaca and guanaco. However, no other VHH molecules that bind to EGFR and/or serum albumin are produced in other species such as camel, dromedary, vicuña, alpaca and guanaco. Other than the single domain antibodies represented by SEQ ID NO: 1-22, the specification does not teach any single domain antibody that binds to EGFR from other species.

With respect to homologous sequence, functional fragment and functional portion of a homologous sequence of the full length single domain antibody or anti-EGFR polypeptide (claims 8-9), the claim encompasses a genus of single domain antibody directed against EGFR for the claimed anti-EGFR polypeptide, any functional portion or any functional portion of any homologous sequence. The specification discloses only single domain antibodies directed against EGFR from llamas. One species is not a representative of the genus Camelidae.

Further, there is insufficient guidance about which amino acids within the full-length sequence of such anti-EGFR polypeptide or single domain antibody derived from any conventional 4-chain antibodies, or engineered antibodies to be substituted, deleted, added or combination thereof such that it still maintains its conformational tertiary structure and binds specifically to EGFR. With respect to "functional portion", it is unclear as to whether the "functional portion" is derived from the same anti-EGFR polypeptide or the same single domain antibody that binds to EGFR since the term "thereof" is not recited in the claims. Even if the "functional portion" is derived from the same anti-EGFR polypeptide or the same single domain antibody that binds to EGFR, there is not a single fragment of the single domain antibody or anti-EGFR polypeptide is functional in the specification as filed. There is no guidance as to any functional equivalents, nor derivatives, nor are there any working examples of altered sequences that retain binding specificity to EGFR, in turn, effective for treating any disorder related to cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung. Let alone preventing any such disorders. Accordingly, enablement is not commensurate in scope with claims that encompass "homologue", "functional portion" or functional portion of any homologue sequence of the full length single chain antibody or anti-EGFR polypeptide.

With respect to therapeutic composition, pharmaceutical composition in the absence of *in vivo* data are unpredictable for the following reasons: (1) the antibody may be due to an inherently short half-life of the antibody; (2) the antibody may not reach the target area such as the cerebrum, the retina because, i.e. the size of the antibody may not be able to cross the blood brain barrier where the antibody has an effect; and (3) other functional properties, known or unknown, may make the antibody unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Evidentiary reference Cortez-Retamozo et al (Int J Cancer 98: 456-462, 2002; PTO 1449) teach to be successful as imaging or therapeutic agent for cancer, antibody-based molecules

should be small enough to reach the tumor-associated antigen but, in the case of therapeutic antibodies, still large enough to remain for apt periods of time in the circulation. Once the mass of the antibody fragment becomes less than 60 kDa, their administration will require careful management to maintain the blood concentrations required to permit diffusion into the tumor (see page 459, col. 2, Discussion, in particular). Cortez-Retamozo et al teach single-domain monovalent camel antibody exhibited serious short comings because of its rapid pharmacokinetic clearance as it has an in vivo half-life ($T_{1/2}$) of approximately 2 hour in blood and concluded that nanobody format (being a 15 kDa protein) is not optimal for in vivo use in cancer treatment (see page 460, Table 1, page 461, col. 2, in particular). In the absence of *in vivo* working example, it is unpredictable which anti-EGFR polypeptide is efficacious in treating tumor, let alone preventing any disorder related to cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung as broadly as claimed.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the lack of in vivo working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

11. Claims 1, 3-9, 13, 19, 21, 23, 25, 27, 29, 31, 33, 36, and 42-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR as set forth in claims 1, and 5-7 for treating and/or preventing and/or alleviating any disorders, any disorders such as any cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung, (2) any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against

any EGFR further comprising any single domain antibody directed against any serum protein, (3) anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR further comprising any single domain antibody as set forth in claim 4, (4) any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR wherein said at least one single domain antibody is any homologous sequence, any functional portion, or any functional portion of any homologous sequence of any full length single domain antibody, (5) any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR wherein said at least one single domain antibody is any homologous sequence, any functional portion, or any functional portion of any homologous sequence of any full length anti-EGFR polypeptide, (6) any kit comprising any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR and Epidermal Growth factor or any fragment thereof, (7) a method for the preparation of a medicament comprising any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR and a carrier, (8) any composition comprising any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR and a suitable pharmaceutical vehicle, (9) any kit comprising any anti-Epidermal Growth Factor Receptor EGFR) polypeptide comprising at least any one single domain antibody directed against any EGFR as set forth in claims 36, 42, and (10) any therapeutic composition comprising any VHH which inhibits the growth of human tumor cells by said VHH binding to Epidermal Growth factor receptor of said human tumor cells and (b) any anti-neoplastic agent as set forth in claims 42-45.

Claim 1 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR.

Claim 3 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least any one single domain antibody directed against EGFR further comprising at least one of any single domain antibody directed against any serum protein.

Claim 4 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least any one single domain antibody directed against EGFR further comprising at least one of any single domain antibody directed against IFN-gamma, TNF-alpha, TNF-alpha receptor, or IFN-gamma receptor.

Claim 5 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least two single domain antibody directed against EGFR.

Claim 6 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least any one single domain antibody directed against EGFR from *Camelidae* VHH.

Claim 7 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least any one humanized *Camelidae* VHH single domain antibody directed against EGFR.

Claim 8 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR wherein said at least one single domain antibody is any homologous sequence, any functional portion, any functional portion of any homologous sequence of the full length single chain antibody.

Claim 9 encompasses any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR wherein the anti-EGFR polypeptide is any homologous sequence, any functional portion, any functional portion of any homologous sequence of the full length single chain antibody.

Claim 13 encompasses a kit comprising any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR and EGFR, or any fragment thereof.

Claims 19, 21, 23, 25, 27, 29, and 31 encompass a method for preparing a medicament comprising combining any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR and a carrier.

Claim 33 encompasses a composition comprising any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR and a suitable pharmaceutical vehicle.

Claims 36 and 42 encompass a kit comprising any anti-Epidermal Growth Factor Receptor (EGFR) polypeptide comprising at least one of any single domain antibody directed against EGFR.

Claims 43-45 encompass a therapeutic composition comprising any VHH which inhibits the growth of human tumor cells by said VHH binding to EGFR and any anti-neoplastic agent.

The specification discloses only isolated single domain antibody VHH from *Camelidae* that binds specifically to Epidermal Growth Factor Receptor (EGFR) such as the ones shown in

Table 4 wherein the antibody comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 1-22. The specification discloses these single domain antibodies selected for binding to EGFR and for the ability to internalize through cell surface EGFR, see page 50. The specification discloses humanized VHH represented by SEQ ID NO: 13, see page 15, lines 9-21. The specification further discloses the isolated single domain antibody VHH from *Camelidae* that binds to EGFR further comprising a single domain antibody VHH that binds to serum albumin corresponds to a sequence selected from the group consisting of SE QI DNO: 27-40 as shown in Table 5. There is no disclosure whether any such anti-EGFR can treat, much less prevent any disorders relating to any cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.).

With the exception of the specific single domain heavy chain antibody VHH that binds to EGFR alone or EGFR and serum albumin as shown in Table 4, there is insufficient written description about the structure associated with function of any and all anti-EGFR polypeptide mentioned above without the amino acid sequence. This is because the definition of single domain antibodies *include, but not limited to*, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies and single domain scaffolds other than those derived from antibodies. Single domain antibodies may be any of the art, or any future single domain antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, goat, rabbit, bovine, see page 13, lines 13-19. A polypeptide without the amino acid sequence has no structure, much less function. The term "comprising" is open-ended. It expands the single domain antibody to include additional amino acids at either or both ends. The term "at least one" encompasses one or more single domain antibody directed against EGFR. Accordingly, the structure of the anti-EGFR polypeptide is not adequately described.

With respect to claim 3, the specification discloses only single domain heavy chain antibody VHH that binds to serum albumin alone or fused to single domain heavy chain antibody

VHH that binds to EGFR. As such, the at least one single domain antibody directed against any serum protein in the claimed anti-EGFR polypeptide is not adequately described. Likewise, the single domain antibody directed against IFN-gamma, TNF-alpha, IFN-gamma receptor and TNF-alpha receptor in the anti-EGFR polypeptide is not adequately described.

With respect to claim 6, the specification discloses antibodies were raised in llamas as one of the *Camelidae* species. The specification defines VHH molecule can be derived from antibodies raised in *Camelidae* species, for example in camel, dromedary, llama, vicuña, alpaca and guanaco. However, no other VHH molecules that bind to EGFR are produced in other species such as camel, dromedary, vicuña, alpaca and guanaco.

With respect to homologous sequence, functional fragment and functional portion of an homologous sequence of the full length single domain antibody or anti-EGFR polypeptide (claims 8-9), not only the structure, i.e., amino acid sequence of any anti-EGFR polypeptides or single domain antibodies are not adequately described, there is insufficient written description about which amino acids within the full-length sequence of any such anti-EGFR polypeptide or single domain antibody can or cannot be substituted, deleted, added or combination thereof such that it still maintains its conformational tertiary structure and binds specifically to EGFR. Further, it is unclear as to whether the "functional portion" is derived from the same anti-EGFR polypeptide or the same single domain antibody that binds to EGFR since the term "thereof" is not recited in the claims. Even if the "functional portion" is derived from the same anti-EGFR polypeptide or the same single domain antibody that binds to EGFR, there is not a single fragment of such single domain antibody or anti-EGFR polypeptide is functional in the specification as filed. As such, any homologous sequence, functional fragment and functional portion of an homologous sequence of the full length single domain antibody or anti-EGFR polypeptide are not adequately described.

With the exception of the specific single domain antibodies that bind specifically to EGFR, or serum albumin or EGFR and serum albumin as disclosed in Tables 4-5, the skilled artisan cannot envision the detailed chemical structure of the encompassed anti-EGFR polypeptide, homologous sequence thereof, functional portion thereof or functional portion of any homologous sequence of the full length single chain antibody or anti-EGFR polypeptide for treating any cancer, much less for preventing any disorders susceptible to modulation by the delivery of any EGFR antagonist, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel,* 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provides only the bovine sequence. In this case, the specification provides the specific sequences for the single domain antibody VHH that bind to EGFR for detection assay, serum albumin and bispecific single domain antibody that binds to EGFR and serum albumin, and seeks coverage for any anti-EGFR polypeptide comprising at least one single domain antibody direct against EGFR, any anti-EGFR polypeptide comprising at least one single domain antibody direct against EGFR and any serum protein, any anti-EGFR polypeptide comprising at least one single domain antibody direct against EGFR and any single domain antibody directed against IFN-gamma, TNF-alpha, IFN-gamma receptor or TNF-alpha receptor, any anti-EGFR polypeptide comprising any homologous sequence or functional fragment of any single domain antibody direct against EGFR, any homologous sequence or functional fragment of any anti-EGFR polypeptide comprising at least one single domain antibody, any VHH that binds to EGFR which inhibits the growth of human tumor cells for treating and preventing any EGFR associated disorders such as any cancer, rheumatoid arthritis, psoriasis, or hypersecretion of mucus in the lung using any polypeptide that is functionally equivalent to such without any *in vivo* data.

Therefore, only the specific single domain VHH antibodies that bind to EGFR for detection assay, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

13. Claims 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "functional portion" in claims 8 and 9 is indefinite because the metes and bounds of what would constitute a "functional portion" cannot be determined. Such is a relative term, and neither the specification nor the claims provide adequate guidance to the interpretation of such term. Further, it is unclear whether such functional portion is derived from the same anti-EGFR polypeptide or single domain antibody.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1, 5, 8-9, 19, 21, 23, 25, 27, 29, 31 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by US Application 2002/0058033 A1 (published May 16, 2002; PTO 1449).

Based on the definition of instant specification at page 13, lines 13-19 that single domain antibodies include, but not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies, single domain antibodies may be any of the art, or any future single domain antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, goat, rabbit, bovine, the claims are interpreted as engineered single chain antibodies derived from conventional 4-chain antibody.

The US application 2002/0058033 A1 teaches an anti-Epidermal Growth Factor Receptor (EGFR) polypeptide such as single-chain antibody clone 6 (scFvs) comprising at least one variable domain from heavy chain that directed against EGFR covalently linked to one variable domain from light chain that directed against EGFR (see entire document, abstract, page 4, paragraphs 0040, 0042, 0059, Figure 1, claims 1-4 of applications, in particular). The

application further teaches pharmaceutical composition comprising the reference antibody and a pharmaceutically acceptable carrier (see page 2, paragraph, 0016, page 4, paragraph 0043, claims 9 and 14 of application, in particular). The term "comprising" is open-ended. It expands the single domain antibody to include additional domain for the claimed anti-EGFR polypeptide to read on the reference anti-EGFR antibody. The term "at least one" implies there is one or more domain of antibody directed against EGFR. The application further teaches homologous sequence of the reference antibody such as clone 63 that binds to EGFR (see Fig 2, in particular). Claims 19, 21, 23, 25, 27, 29 and 31 are included in this rejection because the reference teaches combining the reference antibody in a pharmaceutical acceptable carrier to form a pharmaceutical composition for treating or imaging tumor, see claims 9 and 14 of the application. Thus, the reference teachings anticipate the claimed invention.

16. Claims 1, 5, 13, 36, and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 96/34096 publication (published Oct 1996; PTO 892).

Based on the definition of instant specification at page 13, lines 13-19 that single domain antibodies include, but not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies, single domain antibodies may be any of the art, or any future single domain antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, goat, rabbit, bovine, the claims are interpreted as Fv antibodies derived from conventional 4-chain antibody.

The WO 96/34096 publication teaches an anti-EGFR polypeptide such as Fv antibody fragment from fully-human antibody that binds specifically to EGFR comprising at least one antibody domain from light chain linked to one antibody domain from heavy chain directed against EGFR (see page 6, lines 36-37, page 14, line 25, page 37, line 31, in particular). The term "comprising" is open-ended. It expands the single domain antibody to include additional domain for the claimed anti-EGFR polypeptide to read on the reference anti-EGFR antibody. The term "at least one" implies there is one or more domain of antibody directed against EGFR. The WO 96/34096 publication teaches human antibodies against human TNF-alpha (see page 18, lines 7-16, page 40, line 12, in particular), IFN gamma receptor (see page 37, line 35, gamma interferon (see page 36, line 30, page 39, line 16, in particular) or TNF alpha (see page 40, line 8, in particular). The reference human antibody or binding fragment thereof that reacts with EGFR

avoids the undesired immune response engendered by antibodies or analogs which made from non-human species (see page 13, lines 14-32, in particular). The WO 96/34096 publication teaches a composition comprising the reference antibody fragment or analog and buffer such as sodium acetate buffer (see page 13, lines 7-13, page 25, line 32, in particular).

17. Claims 1, 5, 13, 36, and 42 are rejected under 35 U.S.C. 102(e) as being anticipated by US Application 2002/013275 A1 (published Sept 19, 2002; PTO 892).

Based on the definition of instant specification at page 13, lines 13-19 that single domain antibodies include, but not limited to, heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies, single domain antibodies may be any of the art, or any future single domain antibodies. Single domain antibodies may be derived from any species including, but not limited to mouse, human, camel, llama, goat, rabbit, bovine, the claims are interpreted as Fv antibodies derived from conventional 4-chain antibody.

The application 2002/013275 teaches an anti-EGFR polypeptide such as Fv antibody fragment comprising at least one antibody domain from light chain and one antibody domain from heavy chain directed against EGFR (see page 10, line 0107, page 4, paragraph 0045, page 6, paragraph 0075, in particular). The application 2002/013275 teaches a kit or ELISA kit comprising the reference anti-EGFR polypeptide (see page 16, paragraphs 0179-0182, in particular). The reference ELISA kit may contains the antigen such as EGFR in competition assays (see page 15, paragraph 0166-0167, in particular).

18. Claims 1, 3, 19, 21, 23, 25, 27, 29, 31, 33, and 43-45 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat No 7,300,655 B2 (Filed August 1, 2003 claimed priority to 60/399,707 filed August 1, 2002; PTO 892).

The '655 patent teaches a bispecific antibody fusion protein comprising a single binding domain that binds to Epidermal Growth Factor Receptor (EGFR) polypeptide such as Fv of anti-EGFR and a single domain antibody that binds to serum protein such as alfa-fetal protein wherein the antibody is produced by llamas (see col. 30 lines 14-38, col. 29, lines 20-25, col. 25, lines 35-38, col. 3, line 60-62, in particular). The term "comprising" is open-ended. It expands the single domain antibody to include additional domain for the claimed anti-EGFR polypeptide to read on the reference anti-EGFR antibody. The term "at least one" implies there is one or more domain

of antibody directed against EGFR. The '655 patent teaches single chain Fv molecule comprises at least one domain VL linked to VH (see col. 43, lines 37-64, in particular). Claim 6 is included in this rejection because antibody from llamas is a species of VHH single domain antibody from *Camelidae* whose amino acid sequence is closely resembled of humanized antibody. The '655 patent teaches a composition comprising the reference antibody and a pharmaceutically acceptable carrier for diagnosis (see col. 66, lines 23-56, in particular). Claims 19, 21, 23, 25, 27, 29 and 31 are included in this rejection because the reference teaches combining the reference single chain Fv antibody or bispecific fusion protein in a pharmaceutical acceptable carrier to form a pharmaceutical composition for treating or diagnosing tumor (see col. 40, lines 4-45, col. 43, lines 57-64, col. 67, lines 3-15, in particular). Claim 5 is included in this rejection because the '655 patent teaches the fusion protein may comprise a multiple copies of the same antibody component such as single chain Fv molecule with light chain variable domain linked to heavy chain variable domain (VL-L-VH) where each of the first and second single chain Fv molecules forms a target binding site (see col. 29, lines 59-61, col. 43, lines 41-64, in particular). The '655 patent also teaches a pharmaceutical composition comprising the reference camel antibody, also known as VHH or single domain antibody which binds to EGFR expressed on human tumor cells and an anti-neoplastic agent such as vinca alkaloids, taxol, camptothecans (see col. 48, lines 4-49, in particular). Again, the term comprising is open-ended. It expands the therapeutic composition to include additional antibody to read on the reference composition. The reference composition is administered separately such as before or after administration of the reference antibody for treating liver cancer or hepatocellular carcinoma (see col. 49, lines 1-5, abstract, in particular). Thus, the reference teachings anticipate the claimed invention.

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 1 and 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No 7,300,655 B2 (Filed August 1, 2003 claimed priority to 60/399,707 filed August 1, 2002; PTO 892) in view of WO 96/34096 publication (published Oct 1996; PTO 892) and WO 94/04678 (published March 4, 1994; PTO 892).

The teachings of the '655 patent have been discussed supra. The '655 patent teaches bispecific fusion protein antibody is useful as for the treatment and diagnosis of tumor expressing EGFR such as hepatoblastoma, germ cell tumors, carcinoma (see abstract, in particular).

The invention in claim 4 differs from the teachings of the reference only in that the anti-EGFR polypeptide further comprising at least one single domain antibody selected from the group consisting of anti-IFN-gamma single domain antibody, anti-TNF-alpha single domain antibody, anti-TNF-alpha receptor single domain antibodies, or anti-IFN-gamma receptor single domain antibody.

The WO 96/34096 publication teaches an anti-EGFR polypeptide such as Fv antibody fragment from fully-human antibody that binds specifically to EGFR comprising at least one antibody domain from light chain linked to one antibody domain from heavy chain directed against EGFR (see page 6, lines 36-37, page 14, line 25, page 37, line 31, in particular). The WO 96/34096 publication teaches human antibodies against human TNF-alpha (see page 18, lines 7-16, page 40, line 12, in particular), IFN gamma receptor (see page 37, line 35, gamma interferon (see page 36, line 30, page 39, line 16, in particular) or TNF alpha (see page 40, line 8, in particular). The reference human antibody or binding fragment thereof that reacts with EGFR avoids the undesired immune response engendered by antibodies or analogs which made from non-human species (see page 13, lines 14-32, in particular). The WO 96/34096 publication teaches antibodies and analogs immunoreactive with human TNF-alpha is useful in treating cachexia as well as autoimmune disease such as rheumatoid arthritis, See page 15, line 19-31, in particular). The WO 96/34096 publication teaches antibodies and analogs immunoreactive with human EGFR, TNF-alpha receptor interferon receptor are useful for diagnosis, research and therapy (see page 14, line 21-25, page 13, line 2-5, in particular).

The WO 94/04678 publication teaches method of making single domain antibody such as VHH antibody from camels (see page 13, or new world camelids such as lama paccos, Lama Glama, and Lama vicuña, see page 9, in particular). The reference single domain antibody comprises at least two binding domains such as V_H (see Figure 6, camel IgG, in particular). The WO 94/04678 publication teaches antibodies having different specificities on each heavy polypeptide chains by combining two heavy chains of immunoglobulin from camel or one heavy chain with a fragment of a four-chain model immunoglobulin (see pages 27-28, in particular). The WO 94/04678 publication teaches humanized single domain antibody by replacing camelid specific residues such as amino acid residue at position 45 of VHH for the human 4-chain immunoglobulin (see page 13-14, in particular). The advantages of the single domain antibody from camlids are that it is small in size, and quite soluble (aggregate much less than isolated heavy chains of a four-chain immunoglobulins (see pages 14-15, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to one of ordinary skill in the art to make single domain antibody from camel as taught by WO 94/04678 that binds to human TNF-alpha, IFN-gamma, TNF-alpha receptor or IFN-gamma receptor as taught by WO 96/34096 publication and then substituting the single domain antibody that binds to serum protein alpha fetal protein in the bispecific antibody fusion protein comprising a single binding domain that binds to Epidermal Growth Factor Receptor (EGFR) polypeptide and a single domain antibody that binds to serum protein such as alfa-fetal protein as taught by the '655 patent to form a bispecific anti-EGFR polypeptide comprising at least one single domain antibody that binds to EGFR and one single domain antibody that binds to , IFN-gamma, TNF-alpha receptor or IFN-gamma receptor. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 96/34096 publication teaches antibodies and analogs immunoreactive with human TNF-alpha is useful in treating cachexia as well as autoimmune disease such as rheumatoid arthritis , See page 15, line 19-31, in particular). The WO 96/34096 publication teaches antibodies and analogs immunoreactive with human EGFR, TNF-alpha receptor interferon receptor are useful for diagnosis, research and therapy (see page 14, line 21-25, page 13, line 2-5, in particular). The WO 94/04678 publication teaches the advantages of the single domain antibody from camel are that it is small in size, and quite soluble (aggregate much less than isolated heavy chains of a

four-chain immunoglobulins (see pages 14-15, in particular). The '655 patent teaches bispecific fusion protein antibody is useful as for the treatment and diagnosis of tumor expressing EGFR such as hepatoblastoma, germ cell tumors, carcinoma (see abstract, in particular).

22. Claim 2 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

23. No claim is allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The IFW official Fax number is (571) 273-8300.

25. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Patent Examiner
Technology Center 1600
January 4, 2008